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10/733,776	12/12/2003	Mechthild Rieping	7601/80921	9536

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,776	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13-20 and 22-27* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Claims 11 and 13-27 are pending in the application.

2. Applicant's amendment to the claims, filed on 10/7/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

3. Applicant's amendment to the specification, filed on 10/7/2005, is acknowledged.

4. Receipt of an information disclosure statement, filed on 10/14/2005, is acknowledged.

5. Applicant's arguments filed on 10/7/2005 in response to the Office action mailed on 7/13/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

7. All references cited in the information disclosure statement filed on 10/14/2005 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Claim Objections

8. Claim 16 is objected to in the recitation of "L-amino acid composition of step b)" as step b) of claim 11 does not recite an L-amino acid *composition.* It is suggested that applicant maintain consistency of terminology in the claims by, *e.g.,* replacing "L-amino acid composition of step b)" with "L-amino acid of step b)."

Claim Rejections - 35 USC § 112, Second Paragraph

9. The rejection of claim 24 under 35 U.S.C. 112, second paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicant argues the determination of the time required to reach a "maximum amount" of a desired amino acid is a routine matter.

Applicant's argument is not found persuasive. The examiner does not dispute applicant's assertion that the amount of an L-amino acid can be determined by a routine technique. However, this is not the issue at hand. In this case, it remains unclear as to the amount of an L-amino acid produced by the method of claim 11 that is considered to be a "maximum amount." The specification fails to provide guidance for ascertaining the level of L-amino acid that is considered to be a "maximum amount" and those levels that are not. By virtue of variations in preparation of culture media and biological systems, the "maximum amount" of L-amino acid produced in a single batch will vary as compared to another batch. In other words, a "maximum amount" of L-amino acid produced today will likely be different as compared to the "maximum amount" of L-amino acid produced tomorrow. As such, a skilled artisan would not recognize the intended scope of a "maximum amount" of an L-amino acid. Additionally, it is unclear as

to whether the term refers to a specific L-amino acid, *e.g.* threonine, or whether the term refers to the collective amount of all L-amino acids produced. A skilled artisan would recognize that this distinction is critical in the determination of a "maximum amount" of L-amino acid. It is suggested that applicant clarify the meaning of the term "maximum amount" with respect to the formation of L-amino acid.

Claim Rejections - 35 USC § 112, First Paragraph

10. Claims 11, 13-20, and 22-27 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims are drawn to a process using a genus of *Escherichia* bacteria with an inactivated *yjgF* ORF that encodes SEQ ID NO:2.

Initially, it is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." Claim 11 recites the phrase "the *yjgF* open reading frame of said enterobacterium has been inactivated by one or methods of mutagenesis...wherein said *yjgF* open reading frame encodes the polypeptide of SEQ ID NO:2." The only reference to the term "inactivate" as it occurs in claim 11 is in the specification, beginning at p. 2, l. 32, which discloses "[t]he term 'attenuation' in this connection describes the reduction or elimination of the intracellular activity or concentration of one or more enzymes or proteins in a microorganism which are coded by the corresponding DNA, for example by using a weak promoter or a gene

or allele or ORF, which codes for a corresponding enzyme or protein with a low activity or inactivates the corresponding enzyme or protein or gene or ORF and optionally combining these measures" (italics added for emphasis). Thus, in light of the specification, a skilled artisan can broadly, but reasonably interpret the aforementioned phrase as meaning alteration to the *yjgF* open reading frame, so that the concentration of encoded full-length SEQ ID NO:2 is reduced. In view of this definition, the claims encompass, *e.g.,* mutagenesis of the *yjgF* open reading frame so that it encodes SEQ ID NO:2 with deletion of a single amino acid at the C-terminal end. It should be noted that this interpretation does not preclude variants of a *yjgF* open reading frame that encode polypeptides that may have the same or increased biological activity as compared to SEQ ID NO:2.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the

specification discloses only a single representative species of the genus of recited *Escherichia* bacteria, *i.e.*, MG442ΔyjgF, which is SEQ ID NO:2 with an internal deletion by homologous recombination with the phenotype of increased production of threonine (see specification at p. 25, Example 3). The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In this case, the genus encompasses widely variant species having any deletion, insertional mutagenesis by homologous recombination, and/or mutagenesis with incorporation of a non-sense mutation in a nucleic acid encoding SEQ ID NO:2 that results in a *yjgF* ORF being inactivated, including, *e.g.,* an *Escherichia* bacterium having a mutation to a *yjgF* ORF that results in deletion of a single amino acid of SEQ ID NO:2, wherein the resulting encoded variant has the same or increased activity as compared to SEQ ID NO:2. In this case, there is no recited structure-function relationship associated with the genus of *Escherichia* bacteria with a mutated *yjgF* ORF such that a skilled artisan could distinguish species having an increased production of L-threonine from those that do not. As such, the disclosure of the single representative species of MG442ΔyjgF is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus.

Given the lack of description of a representative number of mutant *Escherichia* bacteria, the specification fails to sufficiently describe the claimed invention in such full,

clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

11. The written description rejection of claims 17-18 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record the reasons stated below. The rejection was fully explained in the previous Office action.

RESPONSE TO ARGUMENT: Applicant argues: 1) the examiner addresses only a portion of a claim limitation or definition, which does not accurately reflect what the claim recites; 2) a single gene is recited and, in most instances, the function of the gene is also mentioned; 3) the specification discloses a reference that supports each of the genes recited in the claims; and 4) when taken in context, the disclosed reference "helps in defining the gene."

Applicant's argument is not found persuasive. While it is acknowledged that the examiner may have used an abbreviated version of the recited nucleic acid, such "paraphrasing" was in the interest of brevity and was not meant to alter the context or definition of a recited term. Also, while the examiner acknowledges that a reference or references corresponding to the recited "gene(s)" is/are disclosed in the specification, the recited "genes" are not so limited to the sequences disclosed therein. In this case, there is no recited structural feature(s) associated with the genus of recited "genes." The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by

function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of "genes," the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the gene species within the genus from other genes such that one can visualize or recognize the identity of the members of the genus. Regarding the "genes" of claim 17, the genus encompasses species that are known in the art and additionally encompasses any mutant and variant thereof. The single disclosed species, *i.e.,* the sequence disclosed in the cited reference, fails to represent the variation within the genus of recited "genes." Regarding the "genes" of claim 18, the definition of "inactivated" as given above has been applied to claim 18. Thus, the genus encompasses species that encode mutant and variant proteins that, *e.g.,* have deletion or insertion of multiple amino acids and maintain or exhibit increased biological activity. Again, the single disclosed species, *i.e.,* the sequence disclosed in the cited reference, fails to represent the variation within the genus of recited "genes." Given the lack of description of a representative number of mutant *Escherichia* bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

12. Claims 11, 13-20, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process using an *Escherichia* bacterium having deletion of all or part of endogenous SEQ ID NO:1, wherein the deletion results in increased production of L-threonine, and optionally wherein the *Escherichia* bacterium overexpresses a nucleic acid as specifically disclosed at pp. 14-18 of the specification, wherein overexpression of the nucleic acid is achieved by transformation of the *Escherichia* bacterium with an expression vector comprising said nucleic acid, or optionally wherein the *Escherichia* bacterium has a mutation or deletion of an endogenous nucleic acid as disclosed at pp. 18-19 of the specification, wherein the expression of the endogenous nucleic acid and the activity of the polypeptide encoded by the endogenous nucleic acid is eliminated by the mutation or deletion, does not reasonably provide enablement for a process using any *Escherichia* bacterium as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors have been considered, only those Factors that are most relevant to the instant rejection are addressed below.

The breadth of the claims: Regarding claim 11, as noted above, the phrase "the *yjgF* open reading frame of said enterobacterium has been inactivated by one or methods of mutagenesis...wherein said *yjgF* open reading frame encodes the polypeptide of SEQ ID NO:2" has interpreted in accordance with MPEP 2111 and in view of the specification as meaning alteration to the *yjgF* open reading frame, so that its ability to encode full-length SEQ ID NO:2 is reduced or eliminated. Accordingly, the claims encompass *Escherichia* bacteria with any mutation(s) to a nucleic acid encoding SEQ ID NO:2 as encompassed by the claim, including mutation(s) that result in an encoded polypeptide that has the same, increased, or decreased activity of the polypeptide of SEQ ID NO:2. Claim 17 encompasses the *Escherichia* of claim 11 further comprising "one or more gene products that are overexpressed," wherein overexpression is achieved by *any*

method that results in increased copy number of the gene or by placing the gene under the control of any "strong promoter." Claim 18 encompasses the *Escherichia* bacterium of claim 11 further comprising inactivation of any of the recited genes, wherein the genes can be present in the genome of the bacterium, outside of the genome, *e.g.,* in a vector, or present in the genome and outside of the genome of the *Escherichia* bacterium. The enablement provided by the specification is not commensurate in scope with the claims with regard to the broad scope of *Escherichia* bacteria, the scope of overexpressed gene products, the method of overexpression, and the scope of inactivated genes. In this case, the specification is enabling for a process using an *Escherichia* bacterium having deletion of all or part of endogenous SEQ ID NO:1, wherein the deletion results in increased production of L-threonine, and optionally wherein the *Escherichia* bacterium overexpresses a nucleic acid as specifically disclosed at pp. 14-18 of the specification, wherein overexpression of the nucleic acid is achieved by transformation of the *Escherichia* bacterium with an expression vector comprising said nucleic acid, or optionally wherein the *Escherichia* bacterium has a mutation or deletion of an endogenous nucleic acid as disclosed at pp. 18-19 of the specification, wherein the expression of the endogenous nucleic acid and the activity of the polypeptide encoded by the endogenous nucleic acid is eliminated by the mutation or deletion.

The nature of the invention: The disclosed invention is a process using an *Escherichia coli* bacterium that has an internal deletion of endogenous SEQ ID NO:1 (specification at p. 25) for the use of achieving enhanced production of L-threonine.

The state of the prior art, the relative skill of those in the art, and the predictability or unpredictability of the art: At the time of the invention, the *E. coli yjgF* ORF was known (specification at pp. 6-7). However, at the time of the invention, no function had been assigned to the protein encoded by the *E. coli yjgF* ORF (specification at p. 6, l. 30). Accordingly, the prior art fails to disclose a method for assaying the activity of the protein encoded by the *yjgF* ORF. Consequently, while methods of altering the sequence of an encoding nucleic acid were known in the art at the time of the invention, the prior art fails to disclose a method by which a skilled artisan could determine whether a variant protein encoded by a mutant of a nucleic acid encoding SEQ ID NO:2 is active or inactive. Also, the specification fails to provide guidance regarding the use of those mutant *Escherichia* bacteria that have a mutation in the "*yjgF* open reading frame" that results in, *e.g.,* increased biological activity of a "*yjgF* open reading frame."

The amount or direction or guidance presented and the presence or absence of working examples: The specification discloses only a single working example of the claimed process, *i.e.,* a process using MG442ΔyjgF (specification at pp. 25-26), wherein the process results in the increased production of L-threonine. The specification provides no other guidance as to mutations encompassed by the claims that result in an inactivation of the "*yjgF* open reading frame." Further, other than increased production of L-threonine, the specification fails to disclose any method by which the inactivation of the "*yjgF* open reading frame" can be ascertained. Also, it is noted that the specification fails to disclose even a single working example of an *Escherichia* having an inactivated

"*yjgF* open reading frame" further having increased expression of the gene(s) of claim 17 or inactivation of the gene(s) of claim 18.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of modifying an encoding nucleic acid were known in the art at the time of the invention, it was not routine in the art to make a variant of a nucleic acid encoding SEQ ID NO:2 having numerous alterations as encompassed by the claims and screening those that maintain or do not maintain the biological activity of SEQ ID NO:2 for those that exhibit increased L-threonine production. Further, it was not routine to increase expression of a desired gene by any method that increases the copy number, *e.g.,* by enhancing expression of a transcription factor that controls gene expression. Also, it was not routine in the art to inactivate all genes encompassed by the claims for those that exhibit increased L-threonine production.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the

experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

13. Status of the claims:

Claims 11 and 13-27 are pending.

Claims 11, 13-20, and 22-27 are rejected.

Claim 21 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Thursday, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656